UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,487	10/29/2003	Peter C. Baciu		7399

7590 10/21/2004

Carlos A. Fisher
ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,487	BACIU ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/1/04, is acknowledged.

2. Claims 11-17 are pending and under consideration.

3. In view of the amendment filed on 10/1/04, only the following rejections are remained.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 11-16 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening an agent which inhibit an angiogenic response comprising contacting an inactive pro form or convertase-activated form of αv integrin subunit, an agent to be tested for the ability to inhibit angiogenesis and metalloprotease MT1-MMP under conditions promoting an increase in activation of the integrin a subunit in the absence of said agent and correlating inhibition of said increase in integrin αv subunit activation with the ability to the agent to inhibit angiogenesis, does not reasonably provide enablement for a method for determining whether an agent will inhibit an angiogenic response comprising a) contacting: I) an inactive pro form or convertase-activated form of an integrin α subunit involved in angiogenesis, ii) an agent to be tested for the ability to inhibit angiogenesis and iii) metalloprotease MT1-MMP, under conditions promoting an increase in activation of the integrin a subunit in the absence of said agent, and b) correlating inhibition of said increase in integrin a subunit activation with the ability of the agent to inhibit angiogenesis in claim 11, wherein the correlating step is accomplished by observing a difference in migration of the activated form versus the inactive form of the alpha subunit in electrophoresis or chromatography in claim 12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 10/1/04, have been fully considered, but have not been found convincing.

Applicant points out that none of the pending claims contain a limitation wherein the claimed method is used only to screen inhibitors of "VEGF-dependent angiogenesis". However, the Examiner never points to the claims when discussing the "VEGF-dependent angiogenesis", further upon reading the claims in light of the specification, it is clear that the specification indeed refers to "VEGF driven angiogenic response" (see the specification on page 9, lines 10-15 in particular). Therefore, Applicant appears to mischaracterize the rejection of record.

> "Conclusions. Integrin expression during neovascularization of rat corneas in response to alkaline injury is restricted to angiogenesis along the VEGF/αvβ5

> pathway in conjunction with α1β1, α2β1 and α5β1 integrins. Expression of MT1- MMP within the invasive angiogenic front further suggest that MT1-MMP is also important in mediating VEGF driven angiogenic response, potentially in conjunction with αvβ5 or β1 integrins which co-distribute with MT1-MMP. The pattern of Integrin expression observed within this study correlates well with a VEGF mediated angiogenic response."

Regarding the cited references, Application contends that the function of these citations in the context of an enablement rejection is not readily apparent. While, applicant did not dispute the facts presented by Bergreson et al and Ratnikov et al and contrary to the applicant assertion, the specification lacks sufficient guidance as to which integrin alpha subunit is involved in angiogenesis when contacted with MT1-MMP. Applicant argues that Bergeron reference and the present specifcation actually supports the enablement of the present claimed method. Applicant submits that Bergeron is said to disclose that 9 of the 18 known subunits undergo post-translational cleavage at a site comprising pairs of basic amino acids. Applicant submits that the specification discloses that a set of α subunits including α3, α4, α5, α6, α7, α8, αv, αE, and αv are capable of activation by MTI-MMP. Applicant argues that the specification provides specific guidance for choosing from among the known α subunits those that are susceptible of cleavage and this guidance is supported by Bergerron.

However, the specification further discloses that the integrin expression during neovascularization of rat corneas in response to alkaline injury is restricted to angiogenesis along the VEGF/αvβ5 pathway in conjunction with α1β1, α2β1 and α5β1 integrins. Expression of MT1- MMP within the invasive angiogenic front further suggest that MT1-MMP is also important in mediating VEGF driven angiogenic response, potentially in conjunction with αvβ5 or β1 integrins which co-distribute with MT1-MMP. Therefore, besides αvβ5, the specification fails to provide guidance as to which other cleavable α subunit would inhibit angiogenesis.

Applicant argues regarding Ratinov et al that the last paragraph, the present specification does not indicate that α2 subunit is so activated. Applicant submits that the specification provides considerable guidance as to those integrin alpha subunits that can be activated by MT1-MMP, and lists among such subunits αv, α3 and α5 subunits. Applicant contends that there is no inconstancy between the specification and this reference. Contrary to Applicant assertions the specification (see last paragraph) discloses α2 integrin to localize at the developing vasculature bed.

Applicant contents that while the specification analyzed integrins α1, α2, β3 and β5 (as well as CD31 MMP-2 an MT1-MMP); the same experimental analysis can be performed using the other known alpha subunits such as subunits α3, α4, α5, α6, α8, α9, α2b, αE and αv as is clearly described in the specification. Such as an assay, may include some experimentation to define those alpha subunits which are involved in angiogenesis. Applicant submits that such experimentation cannot properly be considered undue, or indeed anything other than routine, given the guidance of the specification and the level of knowledge of those skilled in the art.

Applicant is relying upon certain biological activities and the disclosure of a single species ($\alpha v\beta 5$) to support an entire genus (all α subunits including their combination with other β subunits). Further characterization of which alpha subunit is involved in angiogenesis, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. Again, in order to satisfy 112, first paragraph, the specification has to teach how to make and use the α subunits of the invention not how to identify the invention.

6. Claims 11-16 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 8/25/04.

Applicant is not in possession of a method for screening an agent which inhibit an angiogenic response comprising contacting an inactive pro form or convertase-activated form of αv integrin subunit, an agent to be tested for the ability to inhibit angiogenesis and metalloprotease MT1-MMP under conditions promoting an increase in activation of the integrin a subunit in the absence of said agent and correlating inhibition of said increase in integrin αv subunit activation with the ability to the agent to inhibit angiogenesis.

Applicant is not in possession of a method for determining whether an agent will inhibit an angiogenic response comprising a) contacting: I) an inactive pro form or convertase-activated form of an integrin α subunit involved in angiogenesis, ii) an agent to be tested for the ability to inhibit angiogenesis and iii) metalloprotease MT1-MMP, under conditions promoting an increase in activation of the integrin a subunit in the absence of said agent, and b) correlating inhibition of said increase in integrin a subunit activation with the ability of the agent to inhibit angiogenesis in claim 11, wherein the correlating step is accomplished by observing a difference in migration of the activated form versus the inactive form of the alpha subunit in electrophoresis or chromatography in claim 12.

Applicant's arguments, filed 10/1/04, have been fully considered, but have not been found convincing.

Applicant submits that the Office Action mistakes the appropriate law to be applied to the claimed methods. Further, Applicant submits that the reliance on the doctrine of simultaneous conception and reduction to practice in the context of the present method claim is misplaced. Applicants argue that they do not claim that they have invented new compositions whose structure is heretofore unknown. Rather, the claims are drawn to methods using materials (integrin α subunits and MT1-MMP) in conjunction with an agent whose effect on activated integrin alpha-mediated angiogenesis is to be determined. Applicant submits that the NCB Entrez database reveals 65 sequence entries when a search is done using the keyword "MT1-MMP" and 1760 entries when the keyword is "integrin alpha". Applicant submits that both the method steps of the claims and the materials used in them, would be clearly understood by the person or ordinary skill in the art to have been invented by the present applicants as of the priority date of the present application. Applicants submit that they do not claim a genus of

different species, they claim a single general method, thus the cited passage if the PTO final Guidelines on Written Description Requirement is not applicant to the present invention.

While Applicant invention is drawn to methods of using integrin α subunits and MT1-MMP, the examiner notes that the instant methods require the use of products, and if said products do meet the written description requirements, then it follows that the instant method does not meet the written description requiement. In the instant case, there is no described or art-recognized correlation or relationship between the structure of the invention, the α subunits of integrin and it's anti-angiogenic function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of α subunits that are cleavable by MT1-MMP, which retain the features essential to the instant invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 11 and 14-17 stand rejected under 35 U.S.C. 102(b) as being anticipated by Klotz *et al* (Graefes Arch Clin Exp Ophthalmol. 238(1):88-93, January 2000), as is evidenced by Zhang *et al* (Invest Ophthalmol Vis Sci. 2002 Apr;43(4):955-62) for the same reasons set forth in the previous Office Action mailed 8/25/04.

Applicant's arguments, filed 10/1/04, have been fully considered, but have not been found convincing.

Applicant argues in conjunction with case law that in order to anticipate, a single reference must disclose within its four corners each and every limitation of the challenged claim. Applicant further submits that an anticipatory reference must enable the claimed invention. Applicant argues that Zhang et al is not properly cited because the reference is not prior art to the present application and even of Zhang were prior art, the allegedly anticipatory reference, Klotz, may not be combined with another reference in an attempt to make out a prima facie case of anticipation.

While normally, only one reference should be used in making a rejection under 35 U.S.C 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to show that a characteristic not disclosed in the reference is inherent (see MPEP 2131.01 Multiple Reference 35 U.S.C. 102 Rejections). Therefore, the use of the evidentiary reference, Zhang et al, is inconsistence with the MPEP and therefore, proper.

Further, Applicant submits that assuming that MT1-MMP is inherently present in the corneal tissue of Klotz, the other major elements of the claimed method are also messing. Applicant contends that claim 11 requires the presence of an inactive pro form or convertase-activated form

of an integrin a subunit involved in angiogenesis, an agent to be tested for the ability to inhibit angiogenesis, and metalloprotease MT1-MMP, under conditions promoting an increase in activation of the integrin a subunit in the absence of said agent, and correlating inhibition of said increase in integrin α subunit activation with the ability of the agent to inhibit angiogenesis. Applicant submits that Klotz directly measures the angiogenic response of corneal tissue to a test agent, and does not acknowledge the existence of MT1-MMP-cleaved species of the integrin alpha subunits at all.

Contrary to applicant assertions the correlation step (resolution step) is taught by Klotz et al. As stated in the previous office action, Klotz et al further teach that in corneas with silver nitrate burns, systemic cRGDfV treatment showed no significant reduction of vascularization compared with controls and that pellets containing bFGF and LM609 mAb induced significantly less neovasculaization than pellets containing bFGF and control mAb (the resolution step). It is immediately apparent to one skilled in the art that the correlation step taught by Klotz is the same as the claimed correlation step. Specially because "integrin α subunit activation" step is considered inherent step because Zhang et al teach that MT1-MMP expression correlated with the angiogenic response (see pg 960, 2nd col., under Discussion and page 959 under Expression of MT1-MMP and MMP2 in particular) that follow the logic that the "activation of α subunit activation" correlates with the angiogenic response. Therefore, the step of measuring the reduction of vascularization compared with controls is a step of correlating inhibition of increase in integrin α subunit activation with the ability of the antibody to inhibit angiogenesis.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 11-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Klotz *et al*, as is evidenced by Zhang *et al*, in view of Deryugina *et al* (2000) (IDS Ref No.AB) for the same reasons set forth in the previous Office Action mailed 8/25/04.

Applicant's arguments, filed 10/1/04, have been fully considered, but have not been found convincing.

Applicant argues that Klotz et al does not acknowledge the existence of MT1 MMP-cleaved species of the integrin alpha subunits at all, and does not mention observing the presence of such cleaved species as an indication of angiogenic activity, both material elements of all the present claims. Applicant submits that Deryugina discusses MT1-MMP "modification" of the β3 subunit including its higher electrophoretic activity. Applicant submits that Deryugina does not even mention or suggest the cleavage-initiated activation of the integrin alpha subunits, focusing instead on protease cleavage of the integrin β3 subunit. Applicant admits that if the combination of Klotz and Deryugina can be said to suggest anything at all, it would not be an examination of cleaved ingerin alpha, but cleaved integrin β3.

Again the existence and presence of the MT1-MMP in the extracellular matrix (as evidenced by Zhang et al) would lead to the activation of the integrin α subunit. Therefor, the existence of MT1-MMP-cleaved species of the integrin alpha subunit is considered inherent property of the screening method taught by Klotz et al. While the Examiner acknowledges that Deryugina et al does not mention or suggest the cleavage-initiated activation of the integrin alpha subunits, however the issue is that obviousness of the one of ordinary skill in the art at the time the invention was made to recombinantly expressed the MT1-MMP and pro form of the integrin a subunit within the cell and the obviousness to use electrophoresis or chromatography to observe the difference in migration of the activated form versus the inactive form.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
October 14, 2004

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600